Stereoselective β-Hydrogen Elimination from Nickel(II)−*N*-Glycoside Complexes

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Octahedral nickel(II)−*N*-glycoside complexes of glucose, galactose, mannose, and talose were synthesized and analyzed by electrospray ionization (ESI). A resulting tricoordinate species generated from the octahedral complex was subjected to collision-induced dissociation. A highly stereoselective dissociation pathway involving β-hydrogen elimination and cross-ring cleavages was observed in complexes possessing equatorial C-2 substituents. ^{2}H- and ^{13}C-labeling experiments indicate that the hydrogen on C-2 and a labile proton are involved in the β-hydrogen elimination. Additionally, C-4, C-5, and C-6 are shown to be lost from the monosaccharide as a result of the cross-ring cleavages. A mechanism is postulated to explain the stereoselectivity of this dissociation.

Tandem mass spectrometric (MS/MS) analysis of carbohydrates in the presence of metal ions has proven to be an effective method for obtaining important stereochemical information including glycosidic linkage position[1] and monosaccharide substitution patterns.[2] We have recently reported that Ni(II)−*N*-glycoside complexes generated via fast-atom bombardment ionization (FAB) undergo cross-ring cleavages that are characteristic of stereochemical features of the coordinated carbohydrate.[3] Herein we report that when tricoordinate Ni(II)−*N*-glycoside complexes are generated via electrospray ionization (ESI) and subjected to collision-induced dissociation (CID), a particular dissociation pathway involving a highly stereoselective β-hydrogen elimination is observed (Scheme 1). To our knowledge, such β-hydrogen shifts have not been previously observed from metal−carbohydrate complexes.

Four Ni(II)−*N*-glycoside complexes, $Ni(NH_2(CH_2)_3NHC_6H_{11}O_5)_2Cl_2$ (**1**), were synthesized.[3,4] The four aldohexoses utilized in this study are epimeric at either C-2 or C-4 (Table 1). Analysis of the diluted crude reaction mixtures of the four *N*-glycoside complexes via electrospray ionization−mass spectrometry (ESI−MS)[5] showed ions at *m*/*z* 293, which we assign[3] to the tricoordinate complex $[Ni(NH_2(CH_2)_3NHC_6H_{11}O_5) - H]^+$ (**2**).

The product ion spectra obtained following CID of the *m*/*z* 293 precursor ions of the glucose and mannose complexes are shown in Figure 1A,B, respectively. The most obvious difference between the two spectra is the near absence of the ion at *m*/*z* 201 in Figure 1B (Table 1). Of the four complexes examined, this ion is only abundant in the two aldohexoses possessing equatorial C-2 hydroxyl groups, namely glucose and galactose. We propose that the loss of 92 Da is the result of a combination of H_2 and $C_3H_6O_3$ losses, the latter a commonly occurring cross-ring cleavage fragment of monosaccharides.[1−3] In fact, a precursor ion scan of the ion at *m*/*z* 201 showed that ions at *m*/*z* 293 and 291 are the only ones that dissociate to produce *m*/*z* 201; i.e., *m*/*z* 203 is not a precursor of *m*/*z* 201. The ion at *m*/*z* 203 is formed from a different dissociation mechanism involving loss of $C_3H_6O_3$ from *m*/*z* 293 and is currently under investigation.

Table 1. Relative Intensity of *m*/*z* 201 Product Ions

monosaccharide	C-2-OH configuration	C-4-OH configuration	rel int (%) of *m*/*z* 201[a]
D-glucose	equatorial	equatorial	>100
D-galactose	equatorial	axial	~80
D-mannose	axial	equatorial	<5
D-talose	axial	axial	<5

[a] Product ion intensity relative to *m*/*z* 203 product ion.

Isotopic labeling studies were performed to identify the various atoms involved in these losses.[6] Several Ni(II)−*N*-glycoside complexes were synthesized with various forms of mono-^{13}C-labeled glucose (glc-2-^{13}C, glc-3-^{13}C, glc-4-^{13}C, and glc-6-^{13}C), each of which gave rise to an ion at *m*/*z* 294. Collision-induced dissociation of the *m*/*z* 294 ions indicates that the $C_3H_6O_3$ neutral species lost is the contiguous three-carbon fragment containing C-4, C-5, and C-6 (Scheme 1). To determine the source of the H_2 loss, deuterium-labeled complexes were synthesized

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(5) ESI mass spectra were obtained on a VG-Quattro (Micromass, Beverly, MA) triple quadrupole mass spectrometer equipped with a hexapole collision cell. The potential of the capillary was set to 3.3 kV with the counter electrode held at 0.8 kV. The skimmer voltage was set to 40 V. All spectra were obtained with a source temperature of 70 °C. The solvent system used was a 9:1 mixture (by volume) of methanol and water. The solutions were introduced to the source by a high-pressure liquid pump at a flow rate of 4 μL/min. The number of scans collected and averaged together was 5 for conventional mass spectra and 10 for product ion mass spectra. Crude reaction mixtures were diluted 1:1000 with methanol. The final Ni(II)−*N*-glycoside concentration was ca. 40 pmol/μL, assuming a quantitative reaction yield. For all ESI-MS/MS spectra collected, argon was used as the collision gas at a pressure of 1.2×10^{-3} mbar. The precursor ion beam coming out of the gas cell was attenuated by 60%. The collision energy (E_{LAB}) used in the MS/MS experiments was 10 eV.

(6) Product ion spectra of all isotopically labeled complexes are provided as Supporting Information.

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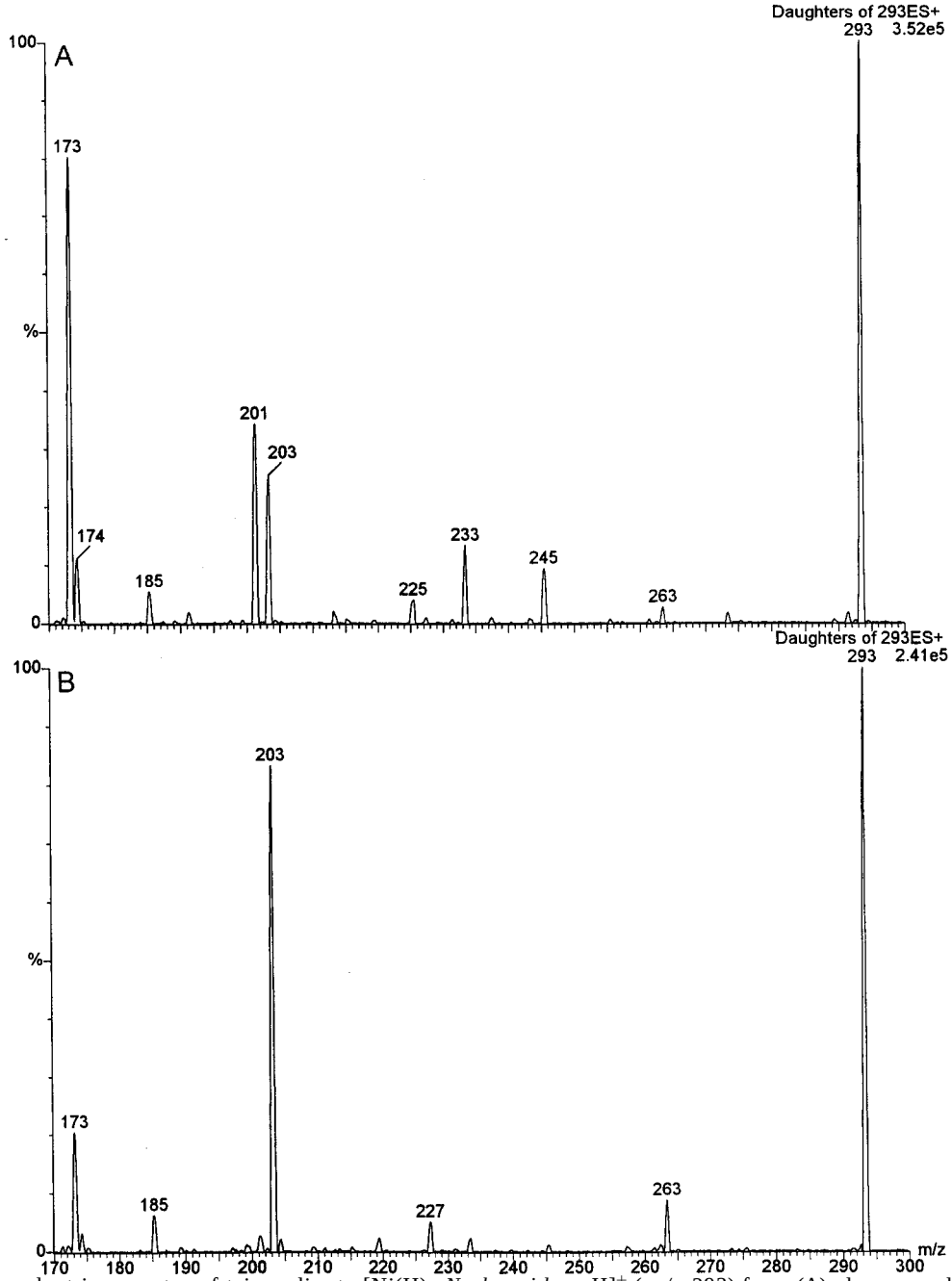
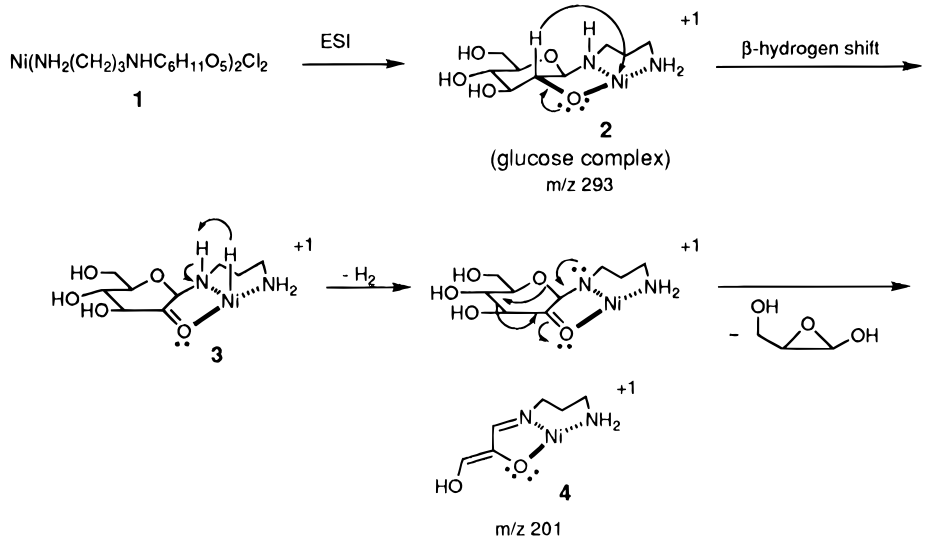


Figure 1. CID product ion spectra of tricoordinate [Ni(II)−*N-glycoside* − H]$^+$ (*m*/*z* 293) from (A) glucose and (B) mannose.

Scheme 1



using both glucose-*1-d* and glucose-*2-d*, which upon electrospray ionization yielded the corresponding tricoordinate ion at *m/z* 294. Collision-induced dissociation of these complexes indicated that the deuterium is lost only from the C-2-labeled complex. Finally, all exchangable hydrogens (i.e., OH, NH and NH_2) were replaced with deuterium by preparing the Ni(II)−*N*-glycoside complex of glucose in CD_3OD. Collision-induced dissociation of the resultant *m/z* 299 ions provided an ion at *m/z* 204, the result of a loss of HD and $C_3H_4D_2O_3$.

On the basis of these labeling experiments, our proposed mechanism for the formation of the *m/z* 201 product ion (Figure 1A) is shown in Scheme 1. Initial generation of the singly charged tricoordinate ion **2** results from loss of one of the tridentate *N*-gylcoside ligands and both chloride ions from **1** and deprotonation of the C-2 hydroxyl group of the remaining ligand. Because of its unusually low coordination number, the unsaturated Ni(II) center is expected to be reactive. β-Hydrogen shift from C-2 of the sugar to the coordinatively unsaturated Ni(II) center would lead to a ketone−hydride intermediate **3**.[7] Literature precedent for β-hydrogen elimination involving late metal alkoxides exists.[8] Loss of H_2 is then proposed to occur via an α-hydrogen abstraction involving the nickel hydride and the proton on the aminal nitrogen. The opportunity for ring opening of the pyranose skeleton now exists, leading to loss of the three-carbon neutral fragment and generation of the Ni(II)-stabilized enolate (**4**).

The fact that the β-hydrogen elimination occurs to a substantial degree from the complexes prepared from glucose and galactose (Table 1), namely the aldohexoses possessing an equatorial C-2 hydroxyl group, implies that the analogous pathway in the epimeric mannose and talose complexes are subject to a significant kinetic barrier.[9] In all of the crystal structures of Ni(II)−*N*-gylcoside complexes,[4] the aminal nitrogen is always equatorial (i.e., β) relative to the other substituents on the monosaccharide. Thus, the mannose and talose complexes possess a cis-orientation of the C-1 and C-2 substituents when bound to nickel. Presumably, the C-2 equatorial hydrogen of these complexes is oriented away from the Ni(II) center, making interaction with a metal-centered d-orbital more difficult than with the C-2 axial hydrogens in the glucose and galactose complexes (see **2** in Scheme 1). Confirmation of this postulate will require further studies on the dynamics of these ions.

Another issue worthy of discussion is the fact that the *m/z* 201 ion is not observed in the metastable ion spectra of any of these complexes that were generated by FAB.[3] This can be rationalized by the fact that β-hydrogen elimination reactions from metallacycles (see Scheme 1), compared to their acyclic analogs, are known to be higher energy processes.[8d,10,11] Although the quantitative energy differences between the *m/z* 293 ions generated by metastable decomposition (FAB ionization) versus collision-induced dissociation (electrospray ionization) are not known, it is valid to state that the latter collision regime is a higher energy process than metastable transitions.

In conclusion, coordinatively unsaturated Ni(II)−*N*-glycoside complexes generated by electrospray mass spectrometry and subjected to CID have been shown to undergo a stereoselective β-hydrogen shift, followed by loss of hydrogen and a three-carbon fragment of the monosaccharide. This method of analysis allows one to readily determine the stereochemistry of aldohexoses at C-2 and provides more evidence that the analysis of stereochemically diverse organic compounds is often greatly enhanced when such molecules are complexed to metal ions. Further gas-phase studies of other coordinatively unsaturated late-metal carbohydrate complexes are underway.

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Supporting Information Available: Product ion spectra of the isotopically labeled complexes (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(7) We propose that a certain population of the *m/z* 293 ions exist as the alkoxide. If the aminal nitrogen was exclusively deprotonated, and ring opening/fragmentation preceded β-hydrogen elimination, then one would expect to see no difference in the intensities of the *m/z* 201 ion between, for example, glucose and mannose since the newly formed C-3 carbanionic intermediates would be enantiomeric.

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(9) The products of β-hydrogen elimination from the glucose or mannose complexes are identical (i.e., intermediate **3** in Scheme 1).

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